PATENT
Docket No.: **2809/1331**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Molino et al.	Examiner: Marcela M. Cordero Garcia
Serial No.	:	10/802,013	
Cnfrm. No.	:	4932	Art Unit: 1654
Filed	:	March 16, 2004	
For	:	NOVEL CYCLOSPORINS	

REQUEST FOR RECONSIDERATION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the outstanding office action, dated January 23, 2007, reconsideration is respectfully requested.

The rejection of claims 1-103 under 35 U.S.C. § 112 (1st para.) for lack of written descriptive support is respectfully traversed.

It is the U.S. Patent and Trademark Office's ("PTO") position that the present application lacks written descriptive support for all compounds encompassed by the claims. In addition, the PTO contends that the amendments to claim 1, filed December 22, 2005, and October 20, 2006, introducing provisos lack written descriptive support and are new matter, because no support was found in the specification for such provisos. Applicants respectfully disagree.

The PTO asserts that no support exists in the present application for amended claim 1 containing the provisos. Applicants submit that there is more than ample basis for a claim of such scope. First, the present application is clearly directed to cyclosporin analogue compounds of the type claimed by the amended claims. The scope of the present invention is apparent from the language of the claims, as described above. Specific compounds according to the claimed invention are set forth in Examples 19-23, 25-29, 31-42, 45-63, 65, 67-73, 75,

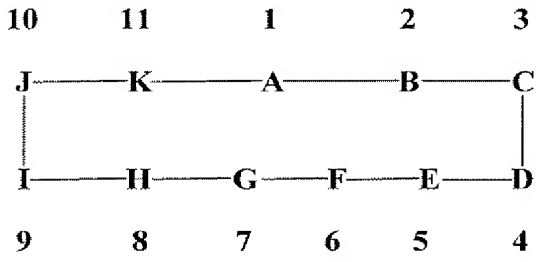
79-80, 85-97, and 108. This is more than sufficient to demonstrate that applicants had possession of the claimed invention. The accompanying Declaration of Bruce F. Molino, Ph.D. under 37 CFR § 1.132 demonstrates that a significant number of compounds in accordance with the claimed invention have immunosuppressive activity.

As to the claimed provisos, *In re Johnson*, 558 F.2d 1008, 194 U.S.P.Q. 187 (C.C.P.A. 1977), the Federal Circuit considered an issue analogous to the one here. In that case, a class of thermoplastic polyarylene polyethers was disclosed and claimed in a U.S. patent application filed in 1963 ("the 1963 application"). *Id.* at 1011, 194 U.S.P.Q. at 190. During prosecution, the 1963 application became involved in an interference that resulted in an award of priority adverse to the inventors. *Id.* at 1012, 194 U.S.P.Q. at 191. In 1972, a continuation-in-part application ("the 1972 application") was filed containing claims which differed from the broad claims of the earlier 1963 application by reciting a proviso that excluded, *inter alia*, two species compounds, i.e., the subject matter of the lost interference count. *Id.* at 1013, 194 U.S.P.Q. at 191. Those claims were rejected by the PTO under 35 U.S.C. § 102 or § 103 on the basis of a Netherlands patent, which was a foreign-filed counterpart of the 1963 application. *Id.* at 1013-14, 194 U.S.P.Q. at 192. While the inventors conceded that the invention was fully disclosed in the Netherlands patent, they contended that the claims are entitled to the benefit of the 1963 filing date under 35 U.S.C. § 120 and therefore the Netherlands patent was not available as a prior art reference. *Id.* at 1014, 194 U.S.P.Q. at 192. The PTO found that the claims were not entitled to the 1963 filing date, because the newly claimed subject matter in the 1972 application was not described in the 1963 application as required by the first paragraph of 35 U.S.C. § 112. *Id.* The PTO Board of Appeals (the "Board") affirmed adding that the artificial subgenus that was created in the 1972 application was not described in the 1963 application, and would be "new matter" if introduced into either the 1963 application or the 1972 application. *Id.* The Court of Customs and Patent Appeals, however, reversed the Board observing that the applicants were merely excising the invention of another, to which they were not entitled, rather than creating an artificial subgenus or claiming new matter. *Id.* at 1019, 194 U.S.P.Q. at 196.

Applicants submit that the PTO's written description rejection in the present application is yet another example of the kind of "hypertechnical application" of the written description requirement of 35 U.S.C. § 112 that was critized by the Federal Circuit in *In re*

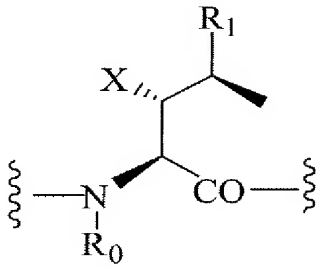
Johnson. Id. See also In re Driscoll, 562 F.2d 1245, 1249, 195 U.S.P.Q.434, 438 (C.C.P.A. 1977).

The present application discloses a class of cyclosporin analogue compounds represented by Formula I, as shown below:



Formula I

wherein A is an amino acid of Formula (II):



Formula II

where:

R_0 is H or CH_3;

R_1 = CHO;
$C(=O)OR_2$;
$C(O)NR_3R_4$;
CH=N-Y;
$CH(NR_5R_6)R_7$;
$CH(OR_8)R_9$;
$CH(OR_{10})_2$;
$CH(SR_{12})_2$;
$CR_{13}R_{14}R_{15}$;
CH=CHC(=O)Me;
$CH_2CH_2C(=O)Me$;
$CH=CHCH(OR_{16})Me$;
$CH_2CH_2CH(OR_{16})Me$;
$CH=CHCH(NR_{17}R_{18})Me$;

$CH_2CH_2CH(NR_{17}R_{18})Me$;
$CH{=}CHC(=N\text{-}Y)Me$;
$CH_2CH_2C(=N\text{-}Y)Me$;
$CH{=}CHC(OR_{19})_2Me$;
$CH_2CH_2C(OR_{19})_2Me$;
$CH{=}CHC(=CR_{20}R_{21})Me$;
$CH_2\text{-}CH_2C(=CR_{20}R_{21})Me$;
$CH{=}CHC(SR_{22})_2Me$;
$CH_2CH_2C(SR_{22})_2Me$;
$CH{=}CR_{23}R_{24}$;
$CH_2CHR_{23}R_{24}$;
$CH{=}CHC(=O)NR_{25}R_{26}$;
$CH_2CH_2C(=O)NR_{25}R_{26}$;
$CH{=}CHC(=O)OR_{26}$;
$CH_2CH_2C(=O)OR_{26}$;
$CH{=}CHC(=O)CH_2CH_2NR_{27}R_{28}$;
$CH_2CH_2C(=O)CH_2CH_2NR_{27}R_{28}$;
$CH{=}CHC(=O)CH{=}CHNR_{29}R_{30}$;
$CH_2CH_2C(=O)CH{=}CHNR_{29}R_{30}$;
$CH{=}CH\text{-}C(OR_{31})R_{32}Me$;
$CH_2CH_2C(OR_{31})R_{32}Me$;
$CH{=}CHC(=O)CH_2C(OH)R_{33}R_{34}$; or
$CH_2CH_2C(=O)CH_2C(OH)R_{33}R_{34}$;

R_2 and R_{26} are the same or different and independently selected from the group consisting of:
hydrogen;
C_1-C_6-straight alkyl chain;
C_3-C_6-straight alkenyl chain;
C_3-C_6-branched alkyl chain;
C_4-C_6-branched alkenyl chain;
C_3-C_6-straight alkynyl chain;
C_3-C_7-cycloalkyl;
CH_2-(C_3-C_7-cycloalkyl);
$(CH_2)_n$-aryl ring;
$(CH_2)_n$-heteroaryl ring;
CH_2OCH_3;
CH_2SCH_3;
CH_2CH_2F;
CH_2CF_3;
$CH_2CH_2CF_3$;
$CH(CF_3)_2$; and
$CH_2OCH_2OC(O)CH_3$;

R_3, R_4, R_5, R_6, R_{10}, R_{11}, R_{12}, R_{17}, R_{18}, R_{19}, R_{22}, R_{25}, R_{27}, R_{28}, R_{29}, and R_{30} are the same or different and independently selected from the group consisting of:
hydrogen;
C_1-C_6-straight alkyl chain;

C_3-C_6-straight alkenyl chain;
C_3-C_6-branched alkyl chain;
C_4-C_6-branched alkenyl chain;
C_3-C_6-straight alkynyl chain;
C_3-C_7-cycloalkyl;
CH_2-(C_3-C_7-cycloalkyl);
$(CH_2)_n$-aryl ring; and
$(CH_2)_n$-heteroaryl ring;

R_3 and R_4, R_5 and R_6, R_{10}, R_{12}, R_{17} and R_{18}, R_{19}, R_{22}, R_{25} and R_{26}, R_{27} and R_{28}, R_{29} and R_{30} are together $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2CH_2-$ that results in the formation of a cyclic moiety that contains the heteroatom or heteroatoms to which they are bound;

R_8, R_{16}, and R_{31} are the same or different and independently selected from the group consisting of:
hydrogen;
C_1-C_6-straight alkyl chain;
C_3-C_6-straight alkenyl chain;
C_3-C_6-branched alkyl chain;
C_4-C_6-branched alkenyl chain;
C_3-C_6-straight alkynyl chain;
C_3-C_7-cycloalkyl;
CH_2-(C_3-C_7-cycloalkyl);
$(CH_2)_n$-aryl ring;
$(CH_2)_n$-heteroaryl ring;
alkanoyl;
alkenoyl;
alkynoyl;
aryloyl;
arylalkanoyl;
alkylaminocarbonyl;
arylaminocarbonyl;
arylalkylaminocarbonyl;
alkyloxycarbonyl;
aryloxycarbonyl; and
arylalkyloxycarbonyl;

R_7, R_9, R_{13}, R_{14}, R_{15}, R_{20}, R_{21}, R_{23}, R_{24}, R_{32}, R_{33}, and R_{34}, are the same or different and independently selected from the group consisting of:
hydrogen;
deuterium;
halogen;
hydroxyl;
nitrile;
substituted and unsubstituted C_1-C_6-straight alkyl chain;
substituted and unsubstituted C_2-C_6-straight alkenyl chain;

substituted and unsubstituted C_3-C_6-branched alkyl chain;
substituted and unsubstituted C_4-C_6-branched alkenyl chain;
substituted and unsubstituted C_2-C_6-straight alkynyl chain;
substituted and unsubstituted C_4-C_6-branched alkynyl chain;
substituted and unsubstituted C_4-C_6-chain having alkenyl and alkynyl groups;
substituted and unsubstituted C_3-C_7-cycloalkyl;
substituted and unsubstituted $(CH_2)_p$-(C_3-C_7-cycloalkyl);
substituted and unsubstituted aryl;
substituted and unsubstituted heteroaryl;
substituted and unsubstituted arylalkyl;
substituted and unsubstituted heteroarylalkyl;
COOH;
$COOR_2$; and
$C(O)NR_3R_4$;

n = 0, 1, 2, 3, or 4;

p = 0, 1, 2, or 3;

X = hydrogen;
hydroxyl; or
hydroxyl group derivatized with an alkanoyl, aryloyl, alkylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, or arylalkyloxycarbonyl group;

Y = C_1-C_6 straight and branched chain alkyl;
C_3-C_6 straight and branched chain alkenyl;
arylalkyl;
heteroarylalkyl;
C_1-C_6 straight and branched chain alkyloxy;
aryloxy;
acyloxy;
arylalkyloxy;
C_1-C_6 straight and branched chain alkylamino;
arylamino;
arylalkylamino;
heteroarylamino;
heteroarylalkylamino;
C_1-C_6 straight and branched chain alkylcarboxamido;
arylcarboxamido;
heteroarylcarboxamido;
C_1-C_6 straight and branched chain alkylsulfonamido;
arylsulfonamido;
arylalkylsulfonamido;
heteroarylsulfonamido;
heteroarylalkylsulfonamido; or
$NH_2C(O)NH$;

CO- in Formula II is covalently bound to an α-amino group of B in Formula I to form an amide linkage, and -N-R_0 in Formula II is covalently bound to a carboxylic acid of K to form an amide linkage;

B is an amino acid selected from the group consisting of:
α–aminobutyric acid;
alanine;
threonine;
valine;
norvaline; and
a modified α–aminobutyric acid, alanine, valine, or norvaline, where a carbon atom in a side chain is substituted with a hydroxyl group;

C is a sarcosine;

D is an amino acid selected from the group consisting of:
leucine;
N-methyl leucine;
valine;
γ-hydroxy-N-methyl leucine; and
γ-hydroxy leucine;

E is an amino acid selected from the group consisting of:
valine;
norvaline; and
a modified valine or norvaline, where a carbon atom in a side chain is substituted with a hydroxyl group;

F is an amino acid selected from the group consisting of:
leucine;
N-methyl leucine;
γ-hydroxy-N-methyl leucine; and
γ-hydroxy leucine;

G is α–aminobutyric acid or alanine;

H is D-alanine;

I and J are independently selected from the group consisting of:
leucine;
N-methyl leucine;
γ-hydroxy-N-methyl leucine; and
γ-hydroxy leucine; and

K is N-methyl valine or valine;

or a pharmaceutically acceptable salt thereof,

with the proviso that: (1) when $R_1 = CH_2CHR_{23}R_{24}$, where R_{23} =H or R_{24} =H, R_{24} or R_{23}, respectively, cannot be substituted C_1-C_6-straight alkyl chain, arylalkyl, halogen, hydroxyl, nitrile, or deuterium or, alternatively when $R_1 = CR_{13}R_{14}R_{15}$, wherein $R_{13} = R_{14} = H$, $R_{13} = R_{15} = H$, or $R_{14} = R_{15} = H$, R_{15}, R_{14}, or R_{13}, respectively, cannot be substituted C_1-C_7-straight alkyl chain; (2) when R_1 = CHO, R_0 cannot be CH_3; (3) when $R_1 = CH{=}CR_{23}R_{24}$, R_{23} and R_{24} cannot be H at the same time and, where R_{23} =H or R_{24} =H, R_{24} or R_{23}, respectively, cannot be substituted and unsubstituted C_2-C_6-straight alkynyl chain; and (4) when $R_1 = CR_{13}R_{14}R_{15}$, wherein $R_{13} = R_{14} = H$, $R_{13} = R_{15} = H$, or $R_{14} = R_{15} = H$, R_{15}, R_{14}, or R_{13}, respectively, cannot be hydrogen, hydroxyl, COOH, unsubstituted C_3-straight alkyl chain, substituted arylalkyl, substituted or unsubstituted C_2-C_6-straight alkenyl or alkynyl chain, or substituted C_3-cycloalkyl. The present application describes the above compounds as immunosuppressive agents.

The amendments to the claims adding provisos simply delete a number of species from the protection sought so that applicants can claim less than the full scope of their original disclosure. As noted in *In re Johnson*, *claiming less* than the full scope of applicants' disclosure is a perfectly legitimate procedure, since "inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable." 558 F.2d at 1018, 194 U.S.P.Q. at 196. *In re Johnson* also noted that "[i]t is for the inventor to decide what *bounds* of protection he will seek." 558 F.2d at 1018, 194 U.S.P.Q. at 196 (quoting *In re Sauders* 444 F.2d 599, 607, 170 U.S.P.Q. 213, 220 (C.C.P.A. 1971)). For the PTO to reject the claims of the present application for lack of written descriptive support would, as stated in *In re Johnson*, "let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed." *Id.*

When the present application contains a broad generic disclosure coupled with extensive examples fully supportive of the limited genus defined by the amended claims containing the proviso, the PTO cannot assert that applicants have failed to disclose and teach those skilled in the art how to make and use the limited genus, i.e., the disclosed genus minus

two of its species, and thus failed to satisfy the written description requirements of 35 U.S.C. § 112. As the Federal Circuit stated in *In re Johnson*,

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species there within, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute.

558 F.2d at 1019, 194 U.S.P.Q. at 196. All that happened here is that applicants narrowed their claims to avoid having them read on prior art. As held in *In re Johnson*, the "written description" in the specification supported the claims in the absence of the proviso and "that specification, having described the whole, necessarily described the part remaining." *Id.* Therefore, the amendments to the claims in the present application indicate that applicants are merely excising the invention of another, to which they are not entitled, and are not creating an artificial subgenus or claiming new matter, as the PTO contends. *Id.*

Accordingly, the rejection under 35 U.S.C. § 112 (1st para.) for lack of written descriptive support is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: July 23, 2007

/Michael L. Goldman/
Michael L. Goldman
Registration No. 30,727

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1304
Facsimile: (585) 263-1600